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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Timothy J. Barberich and James W. Young

Serial No.: 07/896,725 Group Art Unit: 1205

Filed: June 9, 1992 Examiner: L. Schenkman

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231 on 2/10/93

Hamilton, Brook, Smith & Reynolds, P.C.

E. J. Hamil 2/10/93

Signature Date

DECLARATION

To: Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I, Gunnar Aberg, declare:

THAT I am a citizen of Sweden and a resident of the Town of Westborough, Worcester County, Massachusetts;

THAT I am Vice-President of Research and Development, Pharmaceutical Division, Sepracor, Inc., Marlborough, Massachusetts. From 1968 to 1973 I was Director of Pharmacology at Bofors-Nobel Pharma, from 1974 to 1978 I was Group Leader in General Pharmacology at AB Haessle, from 1978 to 1980, I was Director of Pharmacology at Astra Pharmaceuticals, from 1980 to 1982 I was Director of

Cardiovascular Pharmacology at Ciba-Geigy; and from 1982 to 1988 I was Director of Pharmacology, and from 1988 to 1992 Executive Director of Pharmacology, at Bristol-Myers Squibb;

That I am a graduate of the University of Linkoping, Sweden from which I hold a Ph.D. in Pharmacology and of the University of Goteborg, Sweden from which I hold a Ph.D. in Zoophysiology, and that I am an Associate Professor in Applied Pharmacology at the University of Linkoping, Sweden;

That I have twenty-eight years' industrial experience in the area of pharmacology research;

That I am an author of 86 articles on pharmacology, including eight articles on adrenergic β-blockers and β-agonists and that I am an inventor on seven U.S. patents and 6 pending U.S. applications and that I have made numerous presentations before professional societies on the subject of adrenergic drugs;

That I have reviewed carefully the Office Action dated August 10, 1992 in the above case. I have also reviewed the application in the above case and the art cited by the examiner in his rejection, namely Chemical Abstracts 89:123259m (1978), Brittain et al., Harley et al., Hawkins, et al. and Buckner et al.; and as a result of my review and general knowledge of the subject area, I make the following analysis:

The Chemical Abstracts reference teaches that racemic albuterol may be used to treat asthma, but there is no teaching in the reference that would motivate one skilled in the art to go to the considerable trouble and expense of isolating and administering either enantiomer.

Brittain et al. show that both enantiomers and the racemic mixture of albuterol are very selective for β_2 receptors, but the isomeric activity ratio of R and S albuterol on isolated tracheal muscle (β_2) vs atrial muscle (β_1) is "impossible to calculate...because the isomers are virtually inactive on this tissue." R(-) and racemic albuterol inhibited acetylcholine-induced bronchospasm in

anesthetized guinea pigs at dose-levels of 2.5 to 100 μg/kg. The corresponding figure for S(+) albuterol was 50 to 5000 μg/kg, indicating, as expected, a lower potency of the S-isomer. No difference was reported between the effects of R(-) and R,S albuterol in the anesthetized guinea pig. The potency ratio of R(-) vs racemic albuterol could be calculated when the compounds were tested in a model of acetylcholine-enhanced pulmonary resistance in the dog, and indicated that the R(-)-isomer was approximately twice as potent as the racemate. On the isolated guinea pig trachea, Brittain et al. found R-albuterol to be approximately equipotent with the racemate (table 1; page 146). Thus, from a study of the Brittain et al. reference I have not been able to conclude anything definitive regarding either (1) the selectivity of the R isomer vs the racemate, or (2) the relative potencies of the two compounds.

Hartley and Middlemiss teach that both isomers and the racemic mixture of albuterol act on β_2 receptors rather than β_1 receptors. The effects of the R isomer and the racemic mixture are equiactive on β_2 receptors of the intact guinea pig trachea; indeed, it can be calculated from the reported data that the racemate is 1.5 times as potent as the R(-) isomer. There is no clear teaching with regard to selectivity between β_1 and β_2 for the two isomers and the racemate, because the ratio of trachea vs left atrium activity is roughly the same for the R isomer and for the racemate, and the ratio of trachea to right atrium shows a better ratio for the R isomer but partial agonist activity for the R isomer and not for the racemate. Thus, no conclusion can be drawn from Hartley and Middlemiss as to whether the R isomer would enjoy any advantage over racemic albuterol in terms of side effects.

Hawkins and Klease characterize the study of Hartley and Middlemiss by stating that Hartley reported that racemic albuterol was 1.5 times as active as the minus enantiomer. In their studies, Hawkins and Klease found that the R enantiomer was approximately twice as potent as the racemate. They did

not examine any tissue other than guinea pig trachea so that no conclusion relating to relative selectivity could be drawn. Thus if one ignored the teachings of Brittain et al. and particularly of Hartley et al., one could interpret the Hawkins publication to disclose a small potency advantage for the R isomer. On a theoretical basis if the S isomer were totally inactive, the racemate (being a 50-50 mixture) should have a theoretical potency of about 50% that of the R isomer; Hawkins' results would be consistent with that hypothesis.

The study by Buckner and Abel examines the ratio of activity of the R and S isomers of albuterol in guinea pig atria and guinea pig trachea. They concluded "even though the potencies of single isomers may differ as much as twenty-four fold between atria and trachea, the stereoselectivity for production of activity is the same." That is, the selectivity, as measured by the ratio of tracheal to atrial activity, is the same for the two isomers. Buckner did not examine racemic albuterol so no conclusion can be drawn as regards any potency advantage of a single pure R isomer vs the racemate.

The combined teachings of all of the foregoing references provide little clear direction. If one ignores Hartley and one of Brittain's experiments, with the intention of selectively extracting from the references any advantage associated with the R isomer, it appears that the R isomer <u>may</u> enjoy a theoretical two-fold potency advantage over the racemate. However, as a practical matter, even were this the case, it would not motivate a person of scientific skill and experience in the pharmaceutical industry to prepare and administer the pure R isomer instead of the racemate. This is because a process for the resolution of racemic albuterol would inevitably produce R albuterol in less than 50% yield, whereas the use of the racemic albuterol would, at worst, provide 50% of the potency of the pure R. Thus there is little to be gained by resolving the racemate.

As regards the question of diminution of side effects of

R-albuterol vs racemic albuterol, there is no clear teaching in any of the references that R-albuterol would enjoy an advantage over racemic albuterol on the basis of its selectivity between β_1 and β_2 receptors.

In the instant application, Barberich and Young disclose an unexpected diminution in side effects when the pure R isomer of albuterol is administered. Side effects of drugs that have a predominant β_2 agonist component can arise from four presently recognized and well characterized receptor interactions: (a) non-adrenergic effects; (b) interaction of the β-agonist with α-receptors; (c) interaction of the β_2 agonist with β_1 receptors; and (d) interaction of the β_2 agonist with β_2 receptors. The interactions of these drugs with β_3 receptors (the adipocyte β-receptors) have not been well defined and are therefore not discussed in this declaration. Non-adrenergic effects can be triggered by interaction with any of the hundreds of other receptors and by non-receptor interactions, and they can originate from portions of the drug molecule outside the β_2 pharmacophore. They are, for this reason, difficult to predict or screen for. Interaction of β-agonists with α-receptors are known in epinephrine but are not of clinical significance in agonists like albuterol. Interaction of β_2 agonists with β_1-receptors, causing pulmonary agents to exhibit cardiac side effects, is well documented for isoproterenol and has been discussed above for albuterol. The literature cited in the office action provides no evidence for an advantage of either enantiomer of albuterol on the basis of β_2 vs β_1 specificity.

Interaction of β_2-agonists at β_2-receptors can give rise to tachyphylaxis and perhaps to sensitization in addition to the desired bronchodilation. While well documented, these effects are only recently beginning to be understood. Tachyphylaxis appears to arise from mechanisms that are subsequent to the receptor-ligand interaction. [See Strasser et al. Adv. Exp. Med. Biol. 231, 503-517 (1988)]

The recent publications of Morley et al. [Brit. J. Pharmacol. 104, Supp. 295P (1991)] and Chapman et al. [Trends in Pharmacological Science 12 231-232 (1992)], which I have also reviewed, provide newly available support for applicants' disclosure in this respect. The Morley and Chapman references disclose that the S(+) isomer in bronchial tissue causes a hypersensitivity to allergen. This hypersensitivity is not usually observed in acute administration because the bronchodilator effect of the R enantiomer masks the hypersensitivity. However, on subchronic treatment with racemic albuterol Morley et al. were able to detect the hypersensitivity. They concluded from their experiments that the desired bronchodilator effect was prone to tachyphylaxis while the undesirable hypersensitivity is less prone to tachyphylaxis. Indeed, in the Chapman et al. paper the authors recommend that it may be prudent to remove enantiomers that were previously thought to be biologically inert. Their results support a previously undisclosed advantage to the use of pure R enantiomer in that the side effect of paradoxical hypersensitivity is likely to be ameliorated.

I further declare that all statements of the foregoing declaration made of my own knowledge are true and that those made upon information and belief are believed true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Signed by me this 8th day of February 1993.

Gunnar Aberg